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| EXAMINER | |
|---|---|
| KALLIS, RUSSELL | |
| **ART UNIT** | **PAPER NUMBER** |
| 1638 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/614,221 | KARUNANANDAA ET AL. | |
| | Examiner | Art Unit | |
| | Russell Kallis | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 August 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,21 and 25-27* is/are pending in the application.

4a) Of the above claim(s) *6-20and 22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

## DETAILED ACTION

Applicant's election with traverse of Group I in Paper No. 12 is acknowledged. The traversal is on the ground(s) that a serious burden on Examiner would result if the application were restricted. This is not found persuasive because since the inventions of Groups 1-VI have their own separate classification they are distinct and restriction is proper.

The requirement is still deemed proper and is therefore made FINAL.

### *Priority*

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). Application 09/614,221 claims benefit of provisional application 06/142,981 filed 07/12/1999.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 21 rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

Applicant's claim to HES1 protein activity of SEQ ID NO: 622 encoded by an isolated plant polynucleotide from soybean of SEQ ID NO: 1 is based on the degree of DNA sequence identity with DNA isolated in yeast mutation experiments that showed pleiotropic sterol-related phenotypes and wherein the encoded yeast protein showed homology for human oxysterol binding protein (OSBP) (Jiang B. *et al.*, Yeast 1994, March 10, 3:341-353, see Abstract) is not a credible asserted utility.

Computer analysis of genome sequences is currently one of the essential steps for obtaining functional and structural information about the respective gene products, but there are a number of inaccuracies that have been documented by researchers in the field. To illustrate the difficulties, Doerks *et al.*, (TIG, 14: 248-250 1998 pg 248, right column, 2nd paragraph) produces a table of BLAST results from an uncharacterized protein family that includes quite a few proteins with annotations. They state "Only one can give a clue about functional features; others are simply wrong, misleading or uninformative". He continues, "There were even examples in which homologues scored best in PSI-BLAST that did not have the same catalytic activity". It is well established that sequence similarity is not sufficient to determine functionality of a DNA coding sequence. Doerks *et al.* state that computer analysis of genome sequences is flawed, and "overpredictions are common because the highest scoring database protein does not necessarily share the same or even similar functions" (the last sentence of the first paragraph of page 248). Doerks *et al.* also teach homologues that did not have the same catalytic activity because active site residues were not conserved (page 248, the first sentence of the last paragraph). In addition, Smith *et al.* (Nature Biotechnology 15:1222-1223, November 1997) teach "there are numerous cases in which proteins of very different functions are homologous" (page 1222, the first

sentence of the last paragraph). Also, Brenner (TIG 15, 4:132-133, April 1999) discusses the problem of inferring function from homology, stating "most homologs must have different molecular and cellular functions" (see the second full paragraph of the second column of page 132, for example). Furthermore, Bork *et al.* (TIG 12, 10:425-427, October 1996) teach numerous problems with the sequence databases that can result in the misinterpretation of sequence data. Bork *et al.* discussing the same topic state " search methods are stretched and spurious hits are taken as real. Moreover, similarities might only be restricted to certain domains, but the function is transferred to a whole protein" (pg 426, right column, 1st paragraph).

Therefore, given the known errors inherent to functional genomics when relying solely on protein prediction programs, and the lack of quantifiable data demonstrating that SEQ ID NO: 1 encodes a plant HES1 protein, the credibility of the Applicant's specified utility for their invention is not supported in their specification.

Claim 21 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5, 21, 25-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a substantially purified nucleic acid molecule of SEQ ID NO: 1 encoding an amino acid of SEQ ID NO: 622, a substantially purified nucleic acid molecule that specifically hybridizes to a sequence of SEQ ID NO: 1, a substantially purified nucleic acid molecule that specifically hybridizes to a sequence of SEQ ID NO: 1 encoding an amino acid of SEQ ID NO: 622 under high stringency conditions, a substantially purified nucleic acid molecule that specifically hybridizes to a sequence of SEQ ID NO: 1 encoding an amino acid of SEQ ID NO: 622 under low stringency conditions, a substantially purified nucleic acid molecule encoding a plant HES1 protein, and a fragment of the amino acid sequence of SEQ ID NO: 622.

Applicant describes a nucleic acid of SEQ ID NO: 1 encoding an amino acid of SEQ ID NO: 6.

Applicant does not describe any substantially purified nucleic acid molecule encoding SEQ ID NO: 622 other than the nucleic acid of SEQ ID NO: 1, a multitude of substantially purified nucleic acid molecules that specifically hybridize under low stringency conditions to a sequence of SEQ ID NO: 1 encoding an amino acid of SEQ ID NO: 622, any fragments of SEQ ID NO: 1 of a multitude of lengths, and any substantially purified nucleic acid molecules comprising nucleic acid sequences encoding plant HES1 proteins. Therefore, it is not clear that Applicant was in possession of the invention as broadly claimed.

See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the

actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The court also addressed the manner by which genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* At 1406.

5. Claims 1-5, 21, and 25-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant claims a substantially purified nucleic acid molecule of SEQ ID NO: 1 that encodes a protein of SEQ ID NO: 622, a substantially purified nucleic acid that binds under high or low stringency hybridization conditions to said nucleotides, a substantially purified nucleic acid molecule that encodes a plant HES1 protein, and a transformed plant comprising said substantially purified nucleic acid molecule and fragments thereof in sense and antisense orientation.

Applicant teaches the identification of a putative yeast HES1 coding sequence by screening total RNA from soybean, corn, and *Arabidopsis* samples against an array of yeast ORF sequences immobilized on a Nylon membrane (Example 1 page 108-109 and 1$^{st}$ entry of Table 2 page 109), blast homology based identification of putative orthologs to a yeast HES1 coding sequence using normalized (enriched) cDNA libraries from soybean, maize, and *Arabidopsis*

(Example 2 pages 141-154), and a method for tracking changes in sterol production in a plant using radiolabeled acetyl-CoA, squalene, and acetate (Example 3 page 155).

Applicant does not teach the other DNA nucleic acids encompassed by a substantially purified nucleic acid molecule and the substantially purified nucleic acid molecule that encodes a plant HES1 protein, and since Applicant has not taught the encoded protein (presumably an HES1 protein), then they have not taught how to make and/or use DNA encoding a HES1 protein or plants transformed therewith.

The unpredictability of predicting protein function based upon sequence identities that vary within a relatively narrow range can be better understood when considering the methodology used to make such assertions and can be extrapolated from experimental examples where a small number of changes have been introduced into proteins resulted in a change in the substrate preference of an enzyme.

Computer analysis of genome sequences is currently one of the essential steps for obtaining functional and structural information about the respective gene products, but there are a number of inaccuracies that have been documented by researchers in the field. To illustrate the difficulties, Doerks *et al.*, (TIG, 14: 248-250 1998 pg 248, right column, 2nd paragraph) produces a table of BLAST results from an uncharacterized protein family that includes quite a few proteins with annotations. They state "Only one can give a clue about functional features; others are simply wrong, misleading or uninformative". He continues, "There were even examples in which homologues scored best in PSI-BLAST that did not have the same catalytic activity". It is well established that sequence similarity is not sufficient to determine functionality of a DNA coding sequence. Doerks *et al.* state that computer analysis of genome sequences is flawed, and

"overpredictions are common because the highest scoring database protein does not necessarily share the same or even similar functions" (the last sentence of the first paragraph of page 248). Doerks *et al.* also teach homologues that did not have the same catalytic activity because active site residues were not conserved (page 248, the first sentence of the last paragraph). In addition, Smith *et al.* (Nature Biotechnology 15:1222-1223, November 1997) teach "there are numerous cases in which proteins of very different functions are homologous" (page 1222, the first sentence of the last paragraph). Also, Brenner (TIG 15, 4:132-133, April 1999) discusses the problem of inferring function from homology, stating "most homologs must have different molecular and cellular functions" (see the second full paragraph of the second column of page 132, for example). Furthermore, Bork *et al.* (TIG 12, 10:425-427, October 1996) teach numerous problems with the sequence databases that can result in the misinterpretation of sequence data. Bork *et al.* discussing the same topic state " search methods are stretched and spurious hits are taken as real. Moreover, similarities might only be restricted to certain domains, but the function is transferred to a whole protein" (pg 426, right column, 1st paragraph).

The inherent unpredictability in isolation of a homologous sequence encoding the same protein activity is illustrated in an example where a small number of changes to the coding region for a strict desaturase resulted in an enzyme with a hydroxylase activity and that a small number of changes to the coding region of a desaturase could account for the functional divergence seen across a range of enzymes involved in fatty acid metabolism (Broun *et al.* Science Vol. 282 13 November 1998; Abstract lines 4-6 and p. 1317 column 1, lines 51-56).

Given the lack of guidance, the lack of examples in the specification, the breadth of the claims, and the unpredictability in the art, undue trail and error experimentation would have been

required by one skilled in the art to screen through a multitude of homologous nucleic acids and fragments thereof and test for HES1 activity, either *in vivo* or *in planta*.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-5, 21, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At Claims 1-5 and 21, line 1, "substantially purified" is a relative term and therefore is indefinite. Applicant does not indicate what is encompassed by the other nucleic acid molecules representing the substantially purified natural mixture other than SEQ ID NO: 1. Applicant is advised to use art accepted terms, i.e. "An isolated nucleic acid molecule".

At Claim 3, line 1 and all other instances in the claims, "specifically hybridizes" is indefinite. The specification on page 17 defines "specifically hybridizes" as two molecules (DNA) capable of forming an anti-parallel, double stranded nucleic acid structure". This would encompass the partial anti-parallel, double stranded nucleic acid fragments that would occur under low stringency hybridization conditions, i.e. 2X SSC at 50° C.

At Claim 27, line 2, improper Markush terminology is employed, insert --consisting-- before "of" in line 2. See MPEP 2173.05(h).

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 1-5 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Ji *et al.* Plant Physiol., 1994 Feb; 104(2):453-459.

The claims are broad for the reasons discussed supra. In particular, the claims are drawn to a "substantially purified" nucleic acid molecule encoding a soybean protein that ranges from 60% to 95% purification from the other molecules of the native background.

Ji teaches isolation of a soybean cDNA encoding ferric leghemoglobin reductase on page 454 column 1, lines 56-59 and column 2 lines 1-17. Thus, the reference discloses all the limitations of the instant Claims 1-5 and 21.

Claims 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Hubbard *et al.*, WO 97/22703 A2.

The claims are broad for the reasons discussed supra. In particular, the claims are drawn to a plant selected from the group of rapeseed, maize, soybean, safflower, sunflower, cotton, peanut, flax, oil palm, and Cuphea transformed with an antisense RNA to any protein encoding gene or fragment thereof.

Hubbard teaches a maize line carrying and expressing the antisense transcript of starch branching enzyme IIb (Example 7 on page 48, lines 7-9). Thus, the reference discloses all the limitations of the instant Claims 25-27.

***Double Patenting***

10. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v.*

*Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

11. Claims 1-5, 21, 25-26 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-5, 21, 25, and 28 respectively of copending Application No. 10/030,537. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Please see attached sequence search showing instant SEQ ID NO: 622 = copending SEQ ID NO: 30.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claim 27 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 26 of copending Application No. 10/030,537. Although the conflicting claims are not identical, they are not patentably distinct from each other because it would have been obvious to one of ordinary skill in the art to utilize the range of transformed plant species to obtain the instantly claimed range.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. All claims are rejected.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on Monday-Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding, or if the examiner cannot be reached as indicated above, should be directed to the legal analyst, Sonya Williams, whose telephone number is (703) 308-0009.

Russell Kallis Ph.D.
September 25, 2002

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638